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de Jong, C.A.J.; Roozen, H.G.; van Rossum, L.G.M.; Krabbe, P.F.M.; Kerkhof, A.J.F.M.

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High Abstinence Rates in Heroin Addicts by a New Comprehensive Treatment Approach

Cor A.J. De Jong, MD, PhD,[1,2] Hendrik G. Roozen, PhD,[1,3] Leo G.M. van Rossum, MA,[4] Paul F.M. Krabbe, PhD,[4] Ad J.F.M. Kerkhof, PhD[5,6]

[1]Novadic–Kentron, Network for Addiction Treatment Services, Nijmegen, The Netherlands
[2]Nijmegen Institute for Scientist-Practitioners in Addiction, Radboud University Nijmegen, Nijmegen, The Netherlands
[3]Bouman GGZ, Capelle a/d IJssel, The Netherlands
[4]Department of Medical Technology Assessment, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
[5]Department of Clinical Psychology, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands
[6]Research Institute Psychology & Health, Utrecht, The Netherlands

In this multi-center, naturalistic study, the effectiveness of naltrexone maintenance combined with the Community Reinforcement Approach (CRA) was investigated in detoxified, opioid-dependent patients (N=272). Patients were recruited from methadone maintenance programs. With intention-to-treat analysis, 10 months of treatment yielded abstinence rates of 28% and 32% at 10 and 16 months after detoxification. The cumulative abstinence rate at 16 months was 24%. Quality of life, craving, general psychopathology, use of other psychoactive substances, and addiction severity of the abstinent group significantly improved when compared to the relapsed group. This abstinence-oriented approach appears to be a feasible goal, and remains an important option next to long-term methadone maintenance in the management of opioid dependence. (Am J Addict 2007;16:124–130)

INTRODUCTION

An estimated 25,000 heroin-dependent patients live in the Netherlands (16,000,000 inhabitants). About 75% of these addicts are served by addiction treatment centers, particularly by means of methadone maintenance treatment. About 4,500 of the opioid-dependent patients are involved in drug-free treatment. Interventions directed at abstinence are regarded as problematic in terms of high drop-out and high relapse rates and prove to be effective only in a minority of motivated patients under stable living conditions with adequate social support.[1] Given the difficulty of achieving sustained abstinence,[2] there is a tendency to focus on stabilization and harm minimization.[3]

Recent developments in the treatment of opioid-dependent patients aiming at abstinence are promising. In general, detoxification in opioid-dependent patients is not a substitute for treatment but is regarded as the first prominent component in a comprehensive treatment strategy.[4] Detoxification strategies based on antagonist-induced withdrawal seem to be associated with higher initial abstinence rates and with a guaranteed start of naltrexone maintenance treatment.[5] Naltrexone blocks the euphoria induced by opioids and prevents the incentive property of sustained use. Studies on naltrexone maintenance show a clear effect in highly educated and socially well-integrated groups.[6] Pharmacotherapy of opioid addiction is more effective in combination with behavioral and psychosocial approaches,[7,8] although innovative approaches to encourage medication adherence are needed.[9] In the Community Reinforcement Approach (CRA), adherence to medication can explicitly be stimulated. CRA regards behavior as modifiable by positive reinforcement from the individual's real-life community context.[10] In general, there is evidence for the efficacy of CRA, with or without medication, in various substance-related disorders, including alcohol, cocaine, and heroin.[11] The objectives of this study were to determine whether such a comprehensive approach results in high, long-term abstinence rates after successful detoxification in opioid-dependent patients and whether continuously abstinent patients do better than relapsing patients in other domains.

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Address correspondence to Dr. De Jong, Novadic-Kentron, Network for Addiction Treatment Services/Nijmegen Institute for Scientist-Practitioners in Addiction, Radboud University Nijmegen, P.O. Box 9104, 6500 HE Nijmegen, The Netherlands. E-mail: c.dejong@acsw.ru.nl.

METHODS

Study Design and Setting

From four addiction treatment centers in the Netherlands (Novadic, Jellinek, Parnassia, and Kentron), 296 participants were recruited for this study. This is about 9% of the population in treatment concerning opioid dependence in these centers. Twenty-four did not meet the inclusion criteria ($n=5$) or refused to participate ($n=19$). The 272 participants were randomized and allocated to two treatment arms. One treatment consisted of rapid detoxification without anesthesia carried out on an addiction center clinic. The comparative treatment, rapid detoxification under general anesthesia, comprised a complete detoxification in a hospital setting followed by the monitoring of the patients at an addiction center clinic. Rapid detoxification under general anesthesia had no more effect than rapid detoxification without anesthesia.[12] Both detoxification techniques demonstrate a clear reduction of relapse among patients in the withdrawal process. Consequently, both groups were collapsed in further analyses following a naturalistic design. After this standardized inpatient detoxification program of one week, all 272 patients started treatment with naltrexone maintenance and CRA in an outpatient condition. Follow-up was conducted at 1, 10, and 16 months after detoxification.

Participants

All patients were recruited from the standard methadone maintenance programs on a voluntary basis. They had attended these programs for at least a year, were at least 18 years old, and met the diagnostic criteria for opioid dependence according to *Diagnostic and Statistical Manual of Mental Disorders*.[13] They underwent several unsuccessful attempts to become abstinent, expressed their clear wish to become abstinent, and were familiar with the Dutch language. Exclusion criteria were severe somatic diseases or psychiatric disorders, pregnancy, AIDS, doubts about the patient's willingness to cooperate, and contraindications regarding general anesthesia. Patients were not excluded for a dependence on other drugs or drug abuse. However, because of the unpredictable effects of cocaine on the cardiovascular system during anesthesia, treatment was postponed for 48 hours if a patient had used cocaine shortly before detoxification.

Treatment

The CRA protocol encompassed twenty-three sessions. Physicians and psychosocial therapists administered the sessions. This protocol was tailored on the CRA manual of Meyers and Smith.[10] Each of the four treatment sites facilitated a staff to the CRA program that consisted of two physicians and two or three psychosocial therapists, depending on the number of included patients, which varied between 36–86. With respect to the duration of this study (patients were recruited from November 1999 to July 2001), each therapist had a caseload of 10–15 patients. Experienced addiction counselors (social workers and master's-level psychologists) or master's-level psychology students delivered the psychosocial therapy. Experienced physicians delivered medical support and administered naltrexone. Treatment integrity regarding the philosophy of CRA was warranted by a two-day training course prior to the beginning of the study for all CRA physicians and therapists. The CRA methodology was guarded on the basis of notes and stored in files. Furthermore, the second author conducted monthly supervision during the study on each treatment site. For both series, a detailed protocol was available for the treatment by the physician and the psychosocial worker.[14]

In 10 psychosocial sessions, the lifestyle of the patient was assessed and discussed. In these sessions, attention was paid to drug-refusing behavior, relational issues, social counseling, recreational counseling, vocational counseling, problem solving abilities, training in social skills, and craving management. All patients were referred to the first psychosocial session, which was prior to detoxification. The second psychosocial session was administered at discharge of the detoxification procedure. With a frequency of two monthly sessions, the next two sessions were planned. Sessions 5 to 8 were attended monthly, session 9 had an interval of two months, and session 10 had an interval of three months. Each treatment session lasted about 60 minutes.

In 13 sessions, a physician administered and monitored compliance with naltrexone (50 mg dd), addictive behaviors, craving, and the occurrence of adverse events. The first four physician' sessions were planned prior and during the detoxification process. Session five was administered one week after discharge. Sessions 6–7, 8, and 9–13 were planned after 2, 3, and 6 weeks, respectively. Each session lasted about 20 minutes. Subjects had to be accompanied by a non-drug-using coach during treatment, such as a partner, spouse or good friend, who specifically assisted the patient with taking naltrexone.

Assessments

Independent research assistants assessed participants at baseline and during follow-up. The primary outcome measure was defined as self-report of no heroin and/or methadone use in the last 30 days, as verified by urine analysis for opioids at follow-up. The Cumulative Abstinence Duration (CAD) was defined as the period starting after detoxification until the first use of opioids. At baseline and at 16 months, the European version of the Addiction Severity Index[15] was used to assess the severity of seven areas of functioning: medical, employment, alcohol, substances, legal, family/social, and psychiatric. At all assessment points, health domains were measured with the SF-36.[16] The health-related quality of life, based on societal preference values (index) and from the patient

perspective (visual analogue scale, VAS), was measured with the EuroQol-5D.[17] The use of other psychoactive substances and addiction severity was measured with the EuropASI. and urine analyses. Craving was measured with a VAS and general psychopathology with the Symptom Checklist-90.[18]

Data Management and Statistical Methods

An intention-to-treat analysis was performed. To test differences for continuous variables, the general linear model with repeated measures was conducted on continuous variables with baseline levels as a covariate. Missing data considering continuous variables were systematically replaced through analysis provided by the expectation maximization (EM) imputation algorithm. Chi-square tests were applied for dichotomous outcomes and the independent t-test for continuous outcomes. For all statistical analyses, SPSS version 11.5 was used.

RESULTS

After one, ten, and sixteen-month follow-up, data were available for 78, 74, and 86% of the study population. Table 1 shows the details of the patient population at inclusion. Participants attended an average of 6.6 sessions (SD = 3.8) from a physician, received approximately two and one-half months naltrexone, and attended 4.3 (SD = 2.7) sessions of psychosocial CRA therapy.

Figure 1 shows the point prevalence of abstinence and the CAD slope. After a one-month follow-up, 46% of the patients were abstinent for opioids. After 10 and 16 months of follow-up, the point prevalence was 28% and 32%, respectively. The cumulative abstinence duration (CAD) shows a decline in abstinence rates. After 10 and 16 months, 27% and 24% were continuously abstinent, respectively.

Table 2 shows the changes over time for the secondary outcome measures. There was a slight improvement in the general health perception of the SF-36 during the follow-up periods ($F = 9.67$, $p < .001$). The EuroQol-5D index showed a significant beneficial effect during follow-up ($F = 9.05$, $p < .001$). An overall improvement during follow-up was also observed for the EuroQol VAS ($F = 8.48$, $p < .001$). The ASI severity scores showed a significant improvement on all domains except for physical health (see Table 2). In respect to craving, Table 2 shows a minor but statistically significant improvement on the VAS during the follow-up period ($F = 27.0$, $p < .001$). There was a difference between the VAS at intake and month 1 ($p < .001$). Mental health, as measured by the sum score of the SCL-90, showed a significant improvement over time ($F = 9.90$, $p < .001$). All participants had declined in the number of substance-using days during the most recent 30 days, compared to baseline levels (see Table 3).

TABLE 1. Baseline characteristics of the 272 patients

	Mean baseline (SD)
Age (years)	35.9 (6.4)
Male (%)	82.0
Ethnic Dutch (%)	82.9
Employment (%)	
Fully employed	50.2
Part-time employed	10.8
Unemployed	39.0
Marital status (%)	
Single	70
Married	14
Divorced/widowed	16
Education (%)	
Lower	70.8
Secondary	20.4
Higher	8.8
Regular drug use (years)	
Heroin	12.1 (5.9)
Methadone	7.4 (5.7)
Age at first heroin use	20.8 (5.1)
Age at first methadone use	24.1 (7.2)
Number of previous detoxifications	7.9 (8.0)
EuropASI severity scores (0–9)	
Physical health	1.2 (1.5)
Work, education, and income	2.2 (2.3)
Alcohol	.9 (1.7)
Drugs	6.2 (1.1)
Justice/police	1.6 (1.9)
Family/social relations	2.7 (1.8)
Psych/emotional problems	2.1 (1.9)
Gambling	.1 (.6)

Note: Figures are means, standard deviations, and percentages.

There were no significant differences in baseline characteristics between the continuously abstinent and the relapsing group (see Table 4). Table 5 shows the

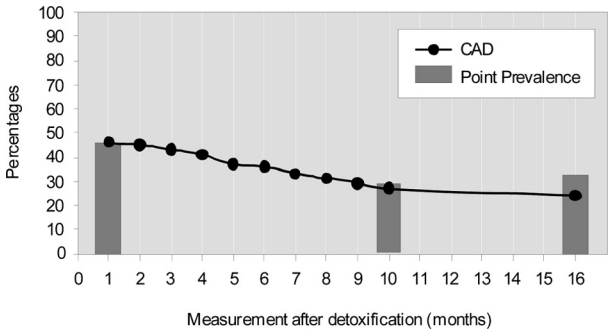

FIGURE 1. Point Prevalence and Cumulative Abstinence Duration (CAD) in Opioid-Dependent Patients at 1, 10, and 16 Months Post-Detoxification

TABLE 2. Secondary outcome measures in detoxified opioid-dependent patients

	Baseline	Month 1	Month 10	Month 16	*p*
Health perception					
General health perception SF-36 (range 0–100)	57.4 (20.1)[a]	63.9 (22.0)[b]	65.4 (22.0)[b]	61.9 (22.8)[b]	< .001
Quality of life					
EuroQol Index (range 0–1)	.74 (.23)[a]	.72 (.25)[b]	.76 (.21)[a]	.76 (.22)[a]	< .001
EuroQol VAS (range 0–100)	68.6 (17.7)[a]	73.6 (18.6)[b]	74.4 (18.3)[b]	74.1 (18.7)[b]	< .001
EuropASI severity scores (range 0–9)					
Physical health	1.1 (1.4)			1.0 (1.6)	.619
Work, education, income	2.2 (2.3)			1.5 (2.2)	< .001
Alcohol	0.9 (1.7)			0.5 (1.3)	.002
Drugs	6.3 (1.0)			3.0 (2.4)	< .001
Justice/police	1.6 (1.9)			.7 (1.6)	< .001
Family/social relations	2.8 (1.8)			1.1 (1.7)	< .001
Psych/emotional problems	2.1 (1.9)			1.7 (2.1)	.021
Craving					
VAS	22.9 (26.5)[a]	7.8 (16.8)[b]	21.7 (30.6)[a]	22.1 (30.1)[a]	< .001
SCL-90					
Total score (range 90–450)	154.9 (49.5)[a]	139.7 (43.4)[b]	140.2 (50.3)[b]	137.4 (49.5)[b]	< .001

Note. Figures are means and standard deviations. Means with different superscripts differ in pair-wise comparisons (SIDAK) at $p < .05$.

comparison of the secondary outcomes between abstinent and non-abstinent patients at 16-month follow-up. Compared with the non-abstinent patients, the abstinent patients had a better health-related quality of life, lower severity scores on the EuropASI (except for alcohol score), lower levels of craving, and lower general psychopathology. The opioid-abstinent group used on significantly fewer days cocaine (1.9 versus 6.3; $p < .01$) days and benzodiazepines (3.6 versus 7.0; $p < .01$) compared with the relapsed patients.

DISCUSSION

This study explored the long-term outcome of opioid antagonist-induced withdrawal in opioid-dependent patients, followed by a comprehensive treatment in which naltrexone maintenance was combined with the Community Reinforcement Approach. Twenty-four percent of participants were persistently abstinent over a 16-month follow-up period.

These positive results can be attributed to the use of the opioid antagonist-precipitated withdrawal techniques, which facilitate the likelihood of successful induction into maintenance naltrexone treatment.[19,20]

The results are in line with the contemporary literature that demonstrates the value of integrating pharmacological agents and cognitive behavioral-oriented therapies that have been widely promulgated to achieve and maintain long-term abstinence in opioid abuse or to prevent relapse.[8,9,21]

The degree of success is much higher than that which could be expected from regular treatment approaches, such as methadone tapering.[2] Most studies have reported upon follow-up periods ranging from one week to one month.[22] More recent reviews suggest that it may not be possible to draw conclusions concerning the long-term effectiveness or cost-effectiveness of withdrawal induced

TABLE 3. Substances used in the past 30 days, according to ASI self-report

Substance	Baseline	Month 1	Month 10	Month 16	F	*p*
Alcohol	6.3 (10.3)	6.0 (8.1)	6.5 (9.1)	6.9 (9.4)	0.42	.74
Heroin	18.4[a] (12.1)	3.0[b] (7.5)	8.3[c] (12.0)	10.3[c] (13.0)	53.88	.00
Methadone	22.9[a] (11.0)	2.9[b] (8.1)	8.2[c] (12.5)	10.6[c] (13.4)	75.73	.00
Opiates (other)	0.1 (1.7)	0.1 (.4)	0.4 (3.1)	0.3 (2.1)	0.79	.50
Medicines	6.0 (11.1)	8.4[a] (11.7)	5.2[b] (10.1)	5.7[b] (10.7)	4.40	.01
Cocaine	4.1 (7.4)	2.3 (5.8)	3.5 (7.7)	4.53 (8.8)	0.83	.48
Amphetamines	.1 (.4)	.0 (.2)	.0 (.2)	.0 (.0)	1.72	.16
Cannabis	7.5 (11.6)	6.8 (1.6)	7.8 (11.7)	8.5 (12.4)	0.65	.58
$\geqslant 1$ substance	18.1[a] (11.9)	4.9[b] (9.0)	8.7[b] (13.2)	10.7[b] (12.6)	39.26	.00

Note. Means with different superscripts differ in pair-wise comparisons (SIDAK) at $p < .05$. Figures are means and standard deviations.

TABLE 4. Baseline characteristics of continuously abstinent (CA) and relapsing patients (R)

	CA	R	*P*
Male (%)	87.7	80.2	.198
Age	35.6 (6.4)	35.9 (6.4)	.710
Health perception EuroQol-5D Index	.75 (.24)	.74 (.23)	.719
VAS	70.2 (17.9)	68.1 (17.7)	.431
Health perception SF-36 General health	59.3 (19.3)	56.8 (20.4)	.382
EuropASI Severity scores (0–9) Physical health	.88 (1.4)	1.3 (1.5)	.089
Work, education, income	2.1 (2.2)	2.3 (2.3)	.547
Alcohol	.73 (1.4)	.92 (1.7)	.448
Drugs	6.3 (1.0)	6.2 (1.1)	.703
Justice/police	1.2 (1.8)	1.7 (1.9)	.100
Family/social relations	2.7 (1.9)	2.7 (1.8)	.914
Psych/emotional problems	2.0 (1.8)	2.1 (2.0)	.567
Gambling	.15 (.79)	.10 (.44)	.675
Craving VAS	19.4 (23.9)	24.0 (27.3)	.243
Mental health SCL-90			
Agoraphobia	9.4 (4.4)	9.9 (3.4)	.461
Anxiety	16.3 (6.9)	16.3 (6.6)	.989
Depression	33.1 (13.5)	31.6 (11.9)	.398
Somatization	20.2 (7.4)	31.6 (11.9)	.782
Insufficiency	16.6 (6.2)	16.4 (6.2)	.823
Interpersonal sensitivity	29.7 (12.3)	28.8 (10.4)	.571
Hostility	9.2 (3.6)	8.8 (3.4)	.372
Insomnia	7.0 (3.6)	6.8 (3.5)	.613
Psychotism	13.6 (4.7)	13.4 (4.5)	.765
Total score	155.0 (54.3)	150.9 (48.0)	.554
Regular drug use (years)			
Heroin	11.5 (.4)	12.2 (6.0)	.442
Methadone	6.6 (5.4)	7.7 (5.8)	.221
Age at first heroin use	21.1 (5.5)	20.8 (5.0)	.643
Age at first methadone use	24.2 (8.6)	24.1 (6.7)	.887
Number of previous detoxifications	7.1 (9.1)	8.1 (7.6)	.370
Substances used in the past 30 days (ASI)			
Alcohol	5.7 (10.3)	6.4 (10.3)	.639
Heroin	17.5 (12.4)	18.7 (12.0)	.525
Methadone	23.1 (11.1)	22.8 (10.9)	.809
Cocaine	3.6 (6.3)	4.3 (7.7)	.537
Cannabis	7.5 (11.7)	7.5 (11.5)	.982
>1 substance	15.6 (11.8)	18.9 (11.8)	.060
Employment (%)			
Fully employed	53.2	49.2	
Part-time employed	14.5	9.6	
Unemployed	32.3	41.1	.344
Marital status (%)			
Single	71.0	69.7	
Married	16.1	13.6	
Divorced/widowed	12.9	16.7	.726
Education (%)			
Lower	77.4	68.7	
Secondary	19.4	20.7	
Higher	3.2	10.6	.177

Note. Figures are means, standard deviations, and percentages.

by opioid antagonists with minimal or heavy sedation or anaesthesia.[5,23] Several recent studies report on long-term outcome, yielding (continuous) abstinence rates ranging from 13 to 80%.[24–32] It is impossible to draw general conclusions from these reports because of the wide variation in study design, objectives, data assessment, sample size, variety in populations, and treatment modalities.

The patients had to bring in a concerned significant other and were characterized by relatively moderate ASI severity scores, especially when compared to treatment-resistant heroin-dependent patients who insufficiently benefit form methadone maintenance treatment.[33] These ASI severity scores ($n = 346$) scores were 3.35 (2.26) for physical health; 4.48 (1.70) for work, education, and income; 1.84 (2.06) for alcohol; 6.11 (.94) for drugs; 4.39 (1.91) for justice and police; 3.60 (1.91) for family and social relations; and 3.54 (3.00) for psychiatric and emotional problems (personal communication, Peter Blanken & Wim van den Brink, 26 January 2006). These scores are up to two times higher than our patient group. It has been shown that naltrexone may be an efficacious adjuvant, especially for (highly) motivated patients who fear the severe consequences of not stopping taking opioids. Such patients may include health care professionals who may be dismissed or parolees who may be returned to prison.[6] Although the population in this study comprised a regular group of patients in a methadone maintenance program who were mostly single and had a low educational level and fifty percent unemployment rate, selection bias cannot be ruled out.

It is noteworthy that abstinence was associated with an improvement in health. Those who did not relapse showed improvements in addictive behaviors, craving, health, and health-related quality of life. Even those who were only temporarily abstinent showed improvement on these outcomes.

No differences in baseline characteristics were found between the group who remained abstinent for 16 months

TABLE 5. Comparison of secondary outcome measures between abstinent and non-abstinent patients at 16-month follow-up

	Abstinent	Non-abstinent	*p*
Health perception			
General health perception SF-36 (range 0–100)	71.8 (21.2)	55.5 (21.5)	.030
Quality of life			
EuroQol Index (range 0–1)	.84 (.17)	.74 (.23)	.010
EuroQol VAS (range 0–100)	81.6 (15.4)	68.9 (19.2)	.013
EuropASI severity scores (range 0–9)			
Physical health	.8 (1.5)	1.2 (1.6)	.06
Work, education, income	.8 (1.5)	2.0 (2.4)	$<.001$
Alcohol	.5 (1.2)	.06 (1.3)	.46
Drugs	.7 (1.3)	4.5 (1.7)	$<.001$
Justice/police	.5 (1.3)	.8 (1.8)	.07
Family/social relations	.7 (1.3)	1.4 (1.8)	$<.001$
Psych/emotional problems	1.1 (2.0)	2.1 (2.3)	.001
Number of attended sessions			
CRA physician	9.19 (2.85)	5.90 (3.78)	$<.001$
CRA psychosocial therapist	5.43 (2.66)	3.91 (2.66)	.002
Naltrexone			
Days received	124.25 (93.73)	57.25 (80.48)	$<.001$

Note. Figures are means and standard deviations.

and those who relapsed. No significant predictors for continued abstinence were found among the large number of characteristics included in the study. Hence, a relative large subgroup of opioid-dependent patients was able to achieve sustained abstinence. Consequently, abstinence as a goal of treatment is attainable for a larger proportion of opioid-dependent patients than has been assumed to date. We would conclude that a relatively large group of patients who are motivated for an abstinence-oriented approach may benefit from the comprehensive series of interventions described in this article.

LIMITATIONS

The design chosen for the add-on effect of general anesthesia in the rapid induction of withdrawal was that of a randomized controlled trial. This was followed by a naturalistic design with a non-randomized evaluation as a major limitation, even though it was performed following recent guidelines for such studies.[34] The study aimed to follow detoxified opioid-dependent patients over a follow-up period of 16 months. This meant that no conclusions could be drawn concerning the causal relationship between the combination of naltrexone and CRA and abstinence in opioid-dependent patients, nor for the differential effect of CRA or naltrexone.

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